

10-  
46-

This Page Is Inserted by IFW Operations  
and is not a part of the Official Record

## BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images may include (but are not limited to):

- BLACK BORDERS
- TEXT CUT OFF AT TOP, BOTTOM OR SIDES
- FADED TEXT
- ILLEGIBLE TEXT
- SKEWED/SLANTED IMAGES
- COLORED PHOTOS
- BLACK OR VERY BLACK AND WHITE DARK PHOTOS
- GRAY SCALE DOCUMENTS

IMAGES ARE BEST AVAILABLE COPY.

As rescanning documents *will not* correct images,  
please do not report the images to the  
Image Problem Mailbox.

**THIS PAGE BLANK (USPTO)**



## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification<sup>6</sup> :

A61K 38/17

A1

(11) International Publication Number:

WO 99/37318

(43) International Publication Date:

29 July 1999 (29.07.99)

(21) International Application Number: PCT/KR99/00037

(22) International Filing Date: 23 January 1999 (23.01.99)

(30) Priority Data:

1998/3362

24 January 1998 (24.01.98)

KR

(71) Applicant (for all designated States except US): SAMYANG GENEX CORPORATION [KR/KR]; 263, Younji-dong, Jongro-ku, Seoul 110-470 (KR).

(72) Inventors; and

(75) Inventors/Applicants (for US only): BAE, Insoo [KR/KR]; Laboratory of Gene Therapy, Samyang Genex Research Institute, 63-2, Hwaam-dong, Yuseong-ku, Daejeon 305-348 (KR). KIM, Dong-Soo [KR/KR]; 134, Yonsei University, College of Medicine, Dept. of Pediatrics, 134, Shinchon-dong, Seodaemun-ku, Seoul 120-752 (KR). YIM, Heajoon [KR/KR]; Laboratory of Gene Therapy, Samyang Genex Research Institute, 63-2, Hwaam-dong, Yuseong-ku, Daejeon 305-348 (KR). JUNG, Neon-Cheol [KR/KR]; Laboratory of Gene Therapy, Samyang Genex Research Institute, 63-2, Hwaam-dong, Yuseong-ku, Daejeon 305-348 (KR). YI, Yong-Weon [KR/KR]; Laboratory of Gene Therapy, Samyang Genex Research Institute, 63-2, Hwaam-dong, Yuseong-ku, Daejeon 305-348 (KR).

HONG, Seung-Shu [KR/KR]; Chounggunarae APT. 109-404, 462-2, Jounmin-dong, Yuseong-ku, Daejeon 305-390 (KR). LEE, Hyun-Soo [KR/KR]; Jewoohouse 101, 550-18, Banpo-dong, Sucho-ku, Seoul 137-040 (KR).

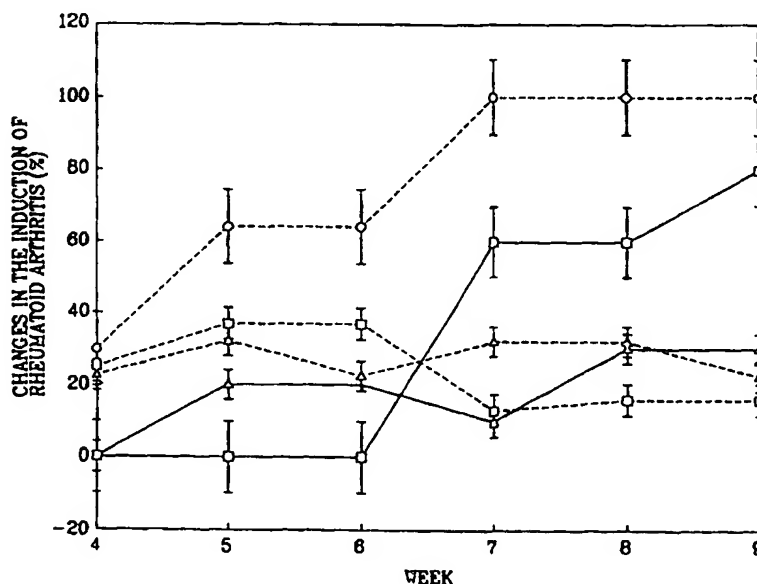
(74) Agent: PARK, Jang, Won; Park, Kim &amp; Partner, Jewoo Building, 4th floor, 200, Nonhyun-dong, Kangnam-ku, Seoul 135-010 (KR).

(81) Designated States: AU, CA, CN, JP, US, European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).

Published

With international search report.

(54) Title: HISTONE CONTAINING COMPOSITION TO TREAT RHEUMATOID ARTHRITIS



(57) Abstract

The present invention relates to a novel use of histone and provides a pharmaceutical composition containing histone as an active ingredient to improve the symptoms of progressive, inflammatory and autoimmune arthritis. The pharmaceutical composition of the present invention includes histone, especially histone H1 as an active ingredient, and could include pharmacologically approved carriers if necessary. Histone H1 lowered induction of arthritis and reduced arthritis index more effectively than steroidal dexamethasone and also had a significant preventive effect.

**FOR THE PURPOSES OF INFORMATION ONLY**

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece	ML	Mali	TR	Turkey
BG	Bulgaria	HU	Hungary	MN	Mongolia	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MR	Mauritania	UA	Ukraine
BR	Brazil	IL	Israel	MW	Malawi	UG	Uganda
BY	Belarus	IS	Iceland	MX	Mexico	US	United States of America
CA	Canada	IT	Italy	NE	Niger	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NL	Netherlands	VN	Viet Nam
CG	Congo	KE	Kenya	NO	Norway	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NZ	New Zealand	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	PL	Poland		
CM	Cameroon	KR	Republic of Korea	PT	Portugal		
CN	China	KZ	Kazakstan	RO	Romania		
CU	Cuba	LC	Saint Lucia	RU	Russian Federation		
CZ	Czech Republic	LI	Liechtenstein	SD	Sudan		
DE	Germany	LK	Sri Lanka	SE	Sweden		
DK	Denmark	LR	Liberia	SG	Singapore		
EE	Estonia						

## HISTONE CONTAINING COMPOSITION TO TREAT RHEUMATOID ARTHRITIS

### TECHNICAL FIELD

- 5 The present invention relates to the use of histone H1 in improving inflammatory symptoms of arthritis. Histone H1 lowers an induction of arthritis and reduces arthritis index more effectively than conventional drugs and also has a significant preventive effect.

### 10 BACKGROUND OF THE INVENTION

The present invention relates to a biologically active compound and compositions containing the same to improve symptoms of progressive, inflammatory and autoimmune arthritis. Despite the development of many arthritis drugs, arthritis  
15 remains to be a world wide serious disease due to an increasing aging population. Even though the death rate due to arthritis is low, the quality of life of an individual who suffers from this disease is sacrificed with lowered activity level and productivity.

- 20 Among many types of arthritis, the most significant one is rheumatoid arthritis. Rheumatoid arthritis is an autoimmune disease by the action of auto-reactive T lymphocytes. T lymphocyte causes rheumatoid arthritis via delayed type hypersensitivity. It is not fully understood which antigen is recognized by T lymphocyte to cause this disease. Type II collagen is known to be the most  
25 probable one, but other possibilities cannot be excluded. Anti-histone autoantibody has been discovered even though it is not clear that this antibody is the cause of the disease.

Many drugs have been used to treat rheumatoid arthritis without a complete relief of the symptoms. Conventional drugs include non-steroidal anti-inflammatory drugs (NSAIDs, aspirin, ibuprofen), gold salt, penicilamine, and steroidal hormones. The

steroidal hormone, which is most potent and effective, have side effects when taken for a long period. Recently, recombinant soluble receptor of tumor necrosis factor (TNF), that play a major role in the inflammation mechanism, is on trial for new treatments of rheumatoid arthritis. However, an improved formulation to treat  
5 symptoms of rheumatoid arthritis such as inflammation, edema, abnormal formation of new blood vessels, destruction of cartilage and bone erosion is required.

Collagen-induced arthritis (CIA) has been used as an animal model of the T-  
10 lymphoidal rheumatoid arthritis (Autoimmunity to Type II collagen: Experimental model of arthritis, J. Exp. Med. 146; 857-868 (1977)). When type II collagen was injected into mice, which are prone to develop arthritis, arthritis was induced within 2 weeks with symptoms such as formation of pannus, erosion of cartilage and bone. Like the rheumatoid arthritis, CIA also has the humoral and the cellular  
15 immune responses against collagen.

Histone is one of the major nuclear components in the cells and forms chromosomes with nucleic acids. Many different forms of histones (H1) were isolated from mammals other than humans. There are many reports regarding  
20 various physiological activities of histone H1.

The discovery and isolation of water-soluble histone H1 in bovine plasma and milk was reported in Biochem. J. Vol. 244, 675-682, 1987. Proc. Natl. Acad. Sci. USA vol. 82, 4871-4875, which reported that the major component of the homeostatic  
25 thymus hormone (HTH) is histone H1. Histone H1 circulates freely in the lymph and blood vessels and acts similar to hormones by having capabilities such as controlling the secretion of other hormones.

Ann. J. Med. Sci. vol. 250, 79-85, 1965 also reported that the HTH therapy could  
30 potentiate the immune system and resolve the immunological problems associated with thymectomy. WO 8503003A suggests using histone H1 fragment, which has



the characteristics of thymus hormone, as an immunotherapy to prevent leukemia after thymectomy or radiotherapy of thymus.

US patent 5,182,257 disclosed histone H1, H2A, H2B, H3 and H4 as drugs for lymphoma or leukemia.

5

Chemical abstracts 74,85743 (1971) reported that, when taken together with T2 bacteriophage, histone H1 subunit could down-regulate the formation of antibodies against T2 bacteriophage. Chemical abstracts 73,96837 (1970) reported the use of histone H1 as an immunosuppressant for skin grafting.

10

Nature vol. 360, 33-39, 1992 reported that histone H1 can stabilize the flagellar microtubule structure of sea urchin. J. Biol. Chem vol. 259,15523-15531, 1984 reported that histone H1, acting with the microtubules isolated from murine brain, induces aggregation of tubulin which is similar to the ring structure of the  
15 microtubules.

No existing references, however, suggests using histone H1 as a drug to treat rheumatoid arthritis.

## 20 BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 is a graph showing the changes in the induction of rheumatoid arthritis after administration of histone H1 (I... I: no treatment after collagen inoculation (control group),  $\Delta$  \_  $\Delta$ : a group that had dexamethasone for a preventive effect,  
25  $\Delta$  ...  $\Delta$ : a group that had dexamethasone for a treatment effect, n - n the group that had histone H1 for a preventive effect, n...n: a group that had histone H1 for a treatment effect).

Figure 2A is a graph showing the preventive effect of histone H1 against  
30 rheumatoid arthritis (I ... I: no treatment after collagen inoculation (control group),  $\Delta$  \_  $\Delta$ : the group that had dexamethasone injection, n - n: a group that had

histone H1 injection).

Figure 2B is a graph showing the treatment effect of histone H1 against rheumatoid arthritis by the changes in arthritis index with time (I... I: no treatment  
5 after collagen inoculation (control group),  $\Delta$  \_  $\Delta$ : the group that had dexamethasone treatment, n - n the group that had histone H1 treatment).

Figure 3A is a picture of a fore leg of a mouse in the control group showing edema at 6 weeks after collagen inoculation.

10

Figure 3B is a picture of a fore leg of a mouse that had histone H1 administration at 6 weeks after collagen inoculation.

Figures 4A and 4B are the sections of knee joints of control group mice showing  
15 the formation of pannus, destruction of cartilage, bone erosion and manifestation of inflammatory cells at 10 weeks after the collagen antigen inoculation (P=pannus, C=cartilage, J= joint space).

Figures 4C is a section of knee joint of a test group mouse that had histone H1  
20 treatment at 10 weeks after the collagen antigen inoculation (P=pannus, C=cartilage, J= joint space).

## SUMMARY OF THE INVENTION

25 It is an object of the present invention to provide a pharmaceutical composition that is more effective than conventional formulations to improve the symptoms of progressive, inflammatory and autoimmune arthritis.

It is an other object of the present invention to provide a pharmaceutical  
30 composition containing histone to improve the symptoms of progressive, inflammatory and autoimmune arthritis.



It is a further object of the present invention to provide a pharmaceutical composition containing histone to prevent the invasion of progressive, inflammatory and autoimmune arthritis.

- 5 It is a further object of the present invention to a method for reducing rheumatoid arthritis symptoms in patients comprising administering histone in a therapeutic effective amount to said patients.

## DETAILED DESCRIPTION OF THE INVENTION

10

The present invention relates to a novel use of histone and provides a pharmaceutical composition containing histone as an active ingredient to improve symptoms of progressive, inflammatory and autoimmune arthritis.

- 15 The symptomatic alleviation includes 1) the improvement of arthritis related symptoms; 2) the prevention of the progress in a progressive disease; and 3) the prevention of invasion in an arthritis prone individual.

The pharmaceutical composition of the present invention comprises histone,  
20 especially histone H1 as an active ingredient, and may include pharmacologically approved carriers if necessary.

The pharmaceutical composition of the present invention may be used by itself or a combination with conventional drugs for arthritis.

25

To determine that the symptoms of autoimmune rheumatoid arthritis could be alleviated by the histone H1 treatment, histone H1 subunit was administered to mammals that were invaded by or prone to arthritis. Collagen induced arthritis, which is a well-known animal model for the rheumatoid arthritis, was induced in  
30 experimental mice (EXAMPLE 1).

In the present invention, mammals can be extended to human and arthritis can be extended into rheumatoid arthritis. There is no limitation in the origin to isolate histone in the present invention. Also, histone can be extended into histone H2A, H2B, H3 and H4 or a mixture thereof.

5

Further, the present invention relates to a method for reducing rheumatoid arthritis symptoms in patients comprising administering histone in a therapeutic effective amount to said patients.

- 10 The required amount of histone H1 enough to prevent the symptoms of arthritis will be determined by an ordinary skilled person in the art without undue experiments.

In the present invention, the interval of administration was 3-4 days, but the interval can be extended to 1, 2 or 4 weeks. The ideal means of administration

- 15 is intravenous or intraperitoneal injection, but other methods can also be used.

The most effective administration route, the amount and the interval of administration could be controlled with ease by observing the degree of symptomatic progress or the reaction of the patient after administration according

- 20 to the diagnosis or the prescription of a doctor.

The invention will be illustrated further by the following examples, but not limited to the examples given.

- 25 To estimate the average values in each experimental group, Student's t-test was used in the examples of the present invention. Chi-square test was used to estimate the standard deviation. The result was considered statistically significant when  $p < 0.05$ .

- 30 EXAMPLE 1. Induction of rheumatoid arthritis in experimental mice

### Induction of arthritis

Five-week old DBA/1J female mice were imported from Charles River Japan and allowed to adapt in an animal room for two weeks before using them in the experiments at the age of 7 weeks (20-25 g).

5

Isolated and quantified type II collagen of chicken (Sigma Chemical Co., St. Louis, MO, USA) was solubilized in 0.1 N acetic acid at a concentration of 2 mg/ml. The solution was mixed with an equal amount of a complete Freund's adjuvant at 4 °C to form a suspension. One hundred microliters of this mixture was injected intravenously around the origin of the tail vein and further inoculated at 3 and 6 weeks after the first injection (D. E. Trentham *et al.*, Autoimmunity to Type II collagen: An Experimental Model of Arthritis, *J. Exp. Med.* 146; 857-868 (1977)). Arthritis was induced from the 4<sup>th</sup> week after the first injection.

### 15 Estimation of arthritis

Clinical incidence of arthritis % (C.I.A) and arthritis index were examined. C.I.A. was expressed as the percentage of mice that have arthritic symptoms among the total mice. The degree of inflammation expressed as the arthritis index was categorized from 0 to 3 by 2 researchers every week as below. Pictures of the feet of some mice were taken 6 weeks after the collagen administration.

- 0: Normal
- 1: Slightly swelling and/or erythema
- 2: Definite edematous swelling
- 25 3: Severe edema and joint rigidity

Arthritis index was calculated for 4 feet (2 hind feet and 2 fore feet) giving the maximum value of 12. The index 6-8 was considered severe since collagen induced arthritis invades in general mainly the hind feet.

### 30 EXAMPLE 2. Extraction and isolation of histone H1

Histone H1 was obtained from Boehringer Mannheim (Catalog Number 223549, lyophilizate, from calf thymus, electrophoretically homogeneous) for the experiment.

EXAMPLE 3. Preventive effect of histone H1 against arthritis

5

Administration of Histone H1

As a test group to examine the preventive effect, 1 mg/kg body weight of histone H1 was administered into 10 mice via intraperitoneal injection 2 times every week from the third week (before arthritis induction) up to 10<sup>th</sup> week after the first  
10 injection. Histone H1 was diluted at a concentration of 5 mg/ml in PBS. As a comparison group, 1 mg/kg body weight of dexamethasone, current available rheumatoid arthritis drug, was administered into 10 mice via intraperitoneal injection 2 times every week from the third week (before arthritis induction) up to 10<sup>th</sup> week after the first injection. As a control group, 300  $\mu$ l of PBS was  
15 administered into 20 mice 2 times every week from the third week up to 10<sup>th</sup> week after the first collagen injection.

Arthritis induction and estimation of arthritis index

Induction of arthritis was observed 4 weeks after the inoculation of antigens in  
20 every group of mice. In the control group that had no treatment after the collagen injection, arthritis induction began 4 weeks after the inoculation (30 %). C.I.A. was 64.3 % at 5<sup>th</sup> and 6<sup>th</sup> weeks and 100 % at the 7<sup>th</sup> week. Compared to this result, the test group of mice that had been injected with histone H1 had a complete prevention of arthritis induction up to the 6<sup>th</sup> week. C.I.A. in the test group was 60  
25 % at 7<sup>th</sup> and 8<sup>th</sup> weeks and 80 % at the 10<sup>th</sup> week. The comparison group of mice that had been injected with conventional dexamethasone had 20 to 30 % of C.I.A. from 4<sup>th</sup> to 10<sup>th</sup> weeks.

Arthritis index for the comparison group was severe with the values of 1.50 0.55 in 4 weeks, 3.00 1.00 in 5 weeks and had the maximum value of 6.00 2.05 in  
30 8 weeks after the antigen inoculation (Figures 2A and 2B). Compared to this result, arthritis in the test group was first observed at the 7th week after the

inoculation having 60 % of the arthritis index of the control group. In the mice that had arthritis, the arthritis index was ca. half of the control group with the values of 2.67 1.15 at 8th weeks and 2.25 1.26 at the 10th week showing that the preventive effect lasts longer than 10 weeks. In the case of dexamethasone injected mice, the arthritis index were 2.00 and 1.50 at 5 and 6 weeks, respectively showing that the preventive effect is lower than histone administration up to 6 weeks.

Estimation of immune reaction: Anti-collagen antibody level

At the 10<sup>th</sup> week the serum was isolated from the blood obtained through a heart puncture. The serum was kept at - 80 °C and thawed immediately before the experiment to measure the anti-collagen antibody level by performing an ELISA (D. E. Tretham & R. A. Dynesius-Trentham, J. Immunol. 130; 2689-2692 (1983)). Type II collagen (25 µg/ml) in 0.1 M PBS was placed in each well of a 96-well polystyrene microplate (Nunc, Denmark) and was incubated at 4 °C for 8 hours. After the incubation, the wells were washed several times with a PBS-0.05 % Tween 20 solution. To prevent non-specific immune reactions, PBS-0.5 % ovalbumin was added in each well and incubated for an hour at room temperature and subsequently washed again with the PBS-0.05 % Tween 20 solution. The serum, diluted 500 times with a buffer solution was added in each well and reacted for 2 hours at room temperature and further washed with the PBS-0.05 % Tween 20 solution. After reacting each well with alkaline phosphatase conjugated goat anti-mouse IgA and IgM for 2 hours and adding 1 mg/ml of p-nitrophenyl phosphate, the absorbance at 450 nm was measured. The anti-collagen antibody level was measured twice for each sample and averaged.

The anti-collagen antibody level for the test group was  $0.588 \pm 0.214$  ( $p < 0.00005$ ) which was significantly lower than the value of  $0.925 \pm 0.075$  for the comparison group. The biological significance, however, is not evident since the anti-collagen antibody level was relatively high in every group.



#### EXAMPLE 4. Arthritis treatment effect of histone H1

##### Administration of histone H1

As a test group to examine the treatment effect, 1 mg/kg body weight of histone H1 was administered into 10 mice via intraperitoneal injection 2 times every week from the 6<sup>th</sup> week (after arthritis induction) up to the 10<sup>th</sup> week. Histone H1 was diluted at a concentration of 5 mg/ml in PBS. As a comparison group, 1 mg/kg body weight of dexamethasone, a currently available rheumatoid arthritis drug, was administered into 10 mice via an intraperitoneal injection 2 times every week from the 6<sup>th</sup> week (after arthritis induction) up to the 10<sup>th</sup> week. Identical control group was used as in EXAMPLE 1.

##### Arthritis induction and arthritis index

C.I.A. in the test group of mice that were treated with histone H1 at the 6<sup>th</sup> week (after arthritis induction) after antigen inoculation was 37.5 % at the 6<sup>th</sup> week and was reduced to 12.5 % at the 7<sup>th</sup> week. This treatment effect lasted up to the 10<sup>th</sup> week with C.I.A. of 14.3 % at 8<sup>th</sup> and 10<sup>th</sup> weeks. In the comparison group that had the dexamethasone treatment, C.I.A. was 22.2 %, 33.3 % and 22.2 % at 7<sup>th</sup>, 8<sup>th</sup> and 9<sup>th</sup> weeks, respectively, showing that the treatment effect was better for histone H1 as a whole.

Arthritis index was 3.33 ± 0.58 at the 5th week after the inoculation for the test group that had the histone treatment. After administration of the histone H1 at the 6th week, the C.I.A remained the same as that at the 5th week however had a reduced arthritis index of 2.67 ± 0.58. After the 7th week, 2/3 of the induced arthritis was completely cured. For the mice that still had the arthritis, the arthritis index decreased to 1.00, 2.00 and 1.00 at 7th, 8th and 10th weeks, respectively, indicating that histone H1 has a significant treatment effect for rheumatoid arthritis that is already in progress. Arthritis index in the comparison group that had the conventional dexamethasone treatment was 2.67, 1.67 and 3.00 at 7th, 8th and 10th weeks, respectively. (Figures 2A and 2B). Pictures of the fore feet of some

of the mice were taken at 6th week after the administration of the collagen. Fore feet of the comparison group had edema, one of the symptoms of arthritis, whereas improvement of edema was observed in the test group that had the histone H1 treatment.

5

#### Estimation of immune reaction: Anti-collagen antibody level

The anti-collagen antibody level was measured to estimate the immune reaction as in EXAMPLE 3. The anti-collagen antibody level for the test group of the treatment effect was  $0.540 \pm 170$  ( $p < 0.00005$ ) which was significantly lower than the  
10 value of  $0.925 \pm 075$  for the comparison group. The biological significance, however, is not evident since the anti-collagen antibody level was relatively high in every group.

#### Pathological observation by H-E staining

15 Mice were sacrificed by blood evacuation from the heart. The legs were cut immediately after the sacrifice and fixed in formalin. After the decalcification, legs were stained by hematoxylin-Eosin. The pathological observation by H-E staining showed that the formation of pannus, the erosion of cartilage and the manifestation of inflammatory cells were observed in 10 weeks after the antigen inoculation in  
20 the sections of the control group (Figures 4A and 4B; P=pannus, C=cartilage, J=joint space).

In comparison, the formation of pannus, the erosion of cartilage or the manifestation of inflammatory cells were not observed in 10 weeks showing a  
25 normal tissue structure in the section of the test group that had the histone H1 treatment (Figure 4C).

What is claimed is :

1. A composition to treat rheumatoid arthritis comprising histone in a therapeutic effective amount.

5

2. The composition according to claim 1 wherein said histone is histone H1.

3. A composition to prevent rheumatoid arthritis comprising histone in a therapeutic effective amount.

10

4. The composition according to claim 3 wherein said histone is histone H1.

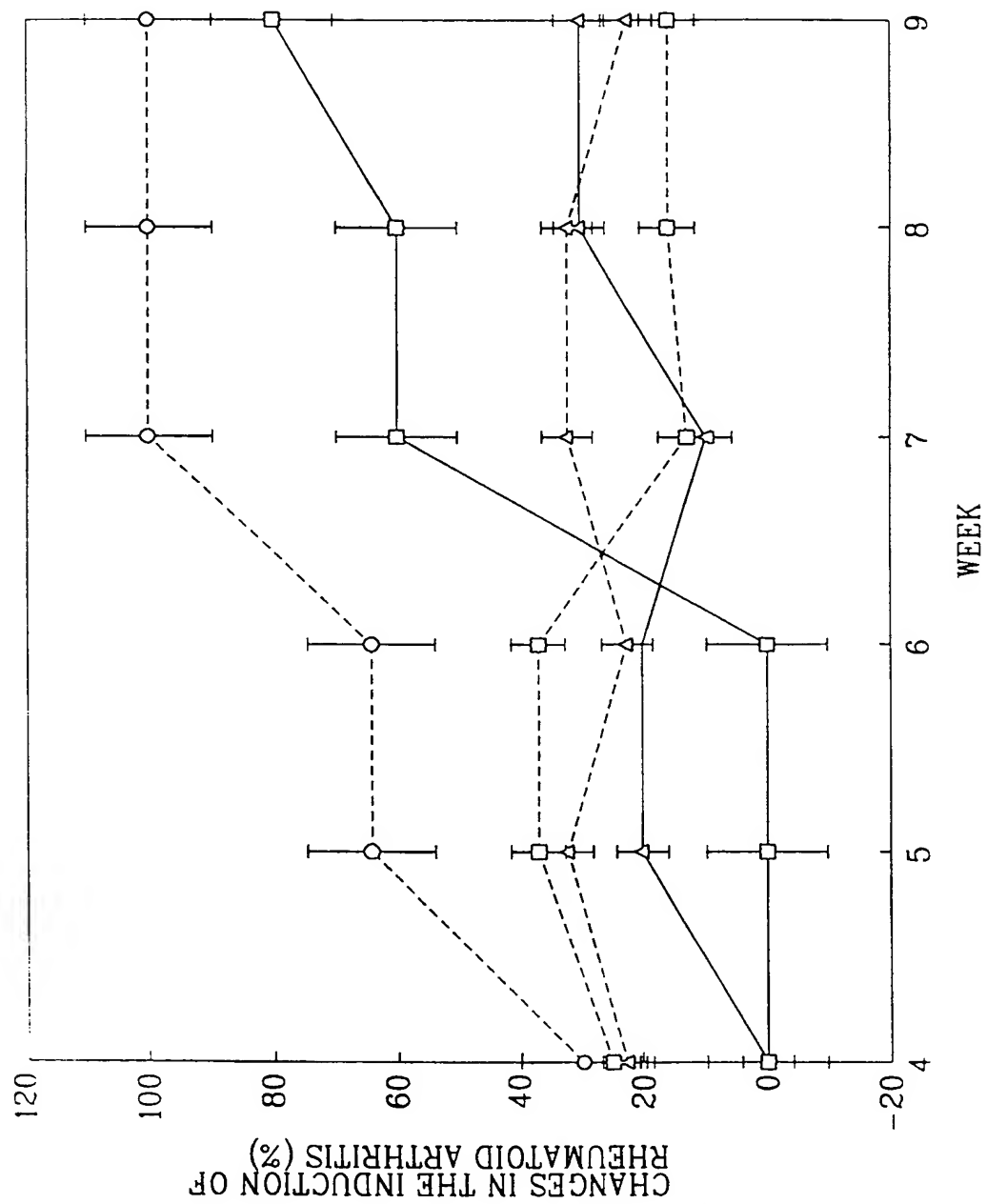
5. A method for reducing rheumatoid arthritis symptoms in patients comprising administering histone in a therapeutic effective amount to said patients.

15



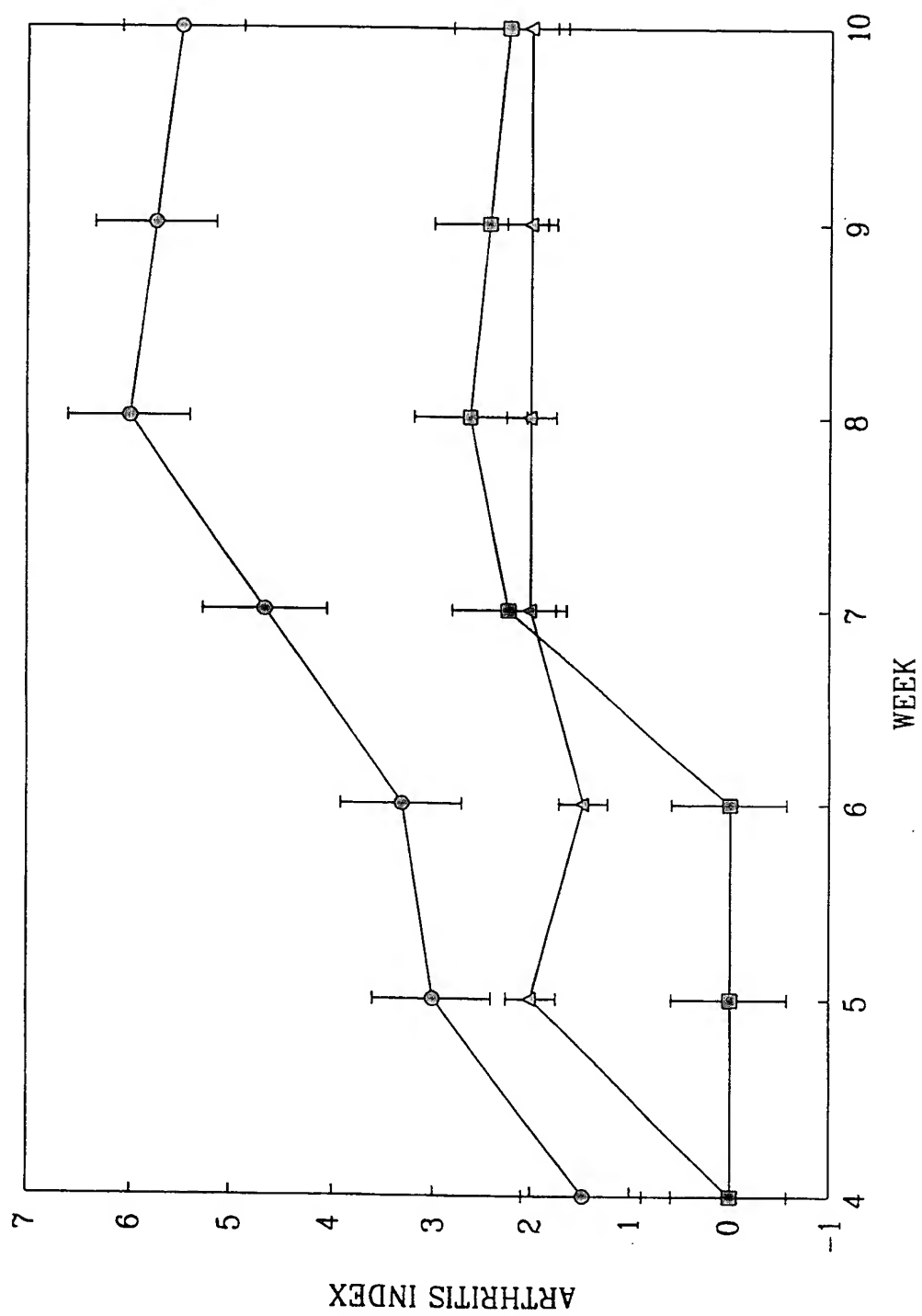
1/6

FIG. 1



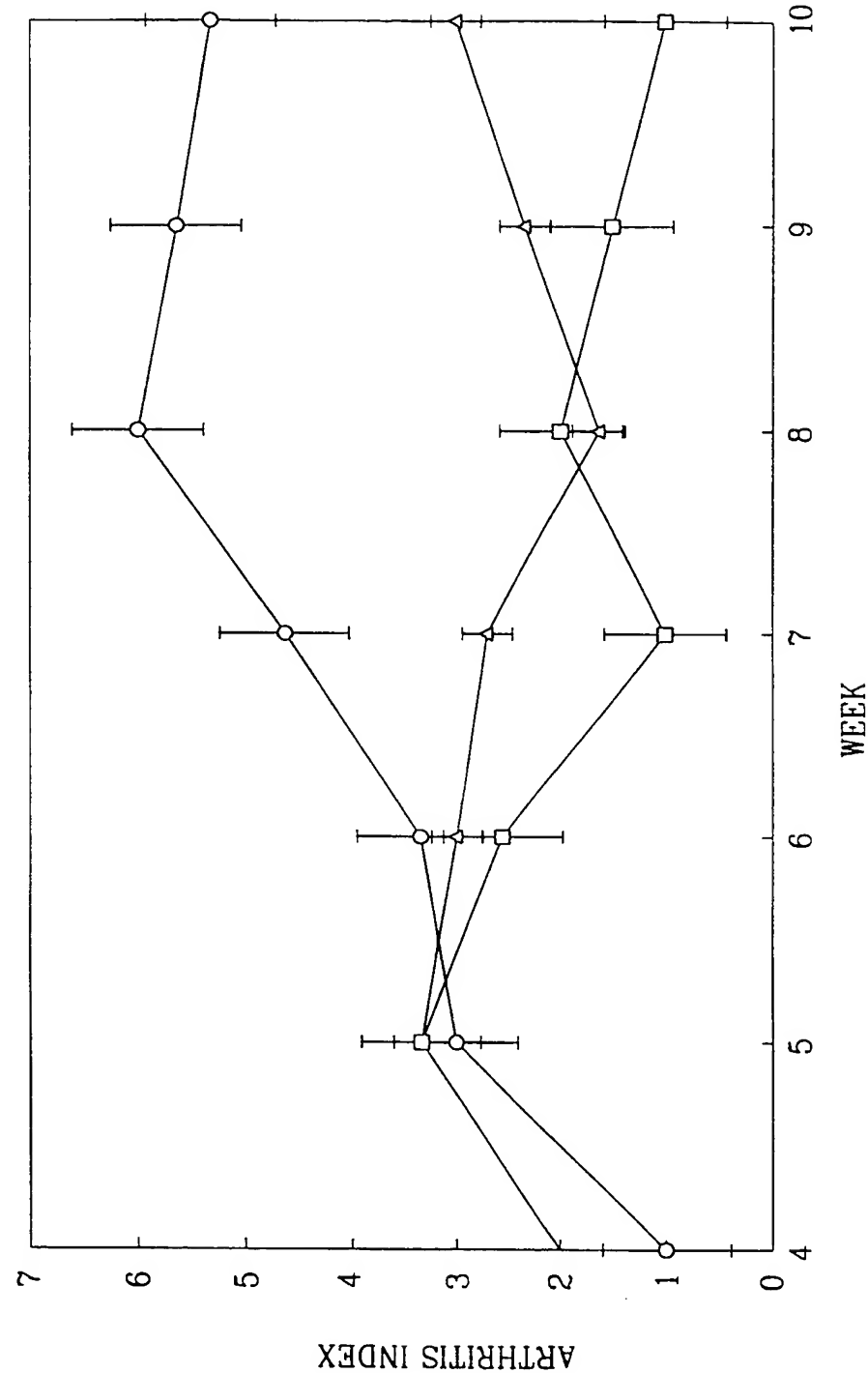
2/6

FIG. 2A



3/6

FIG.2B



4/6

FIG.3A

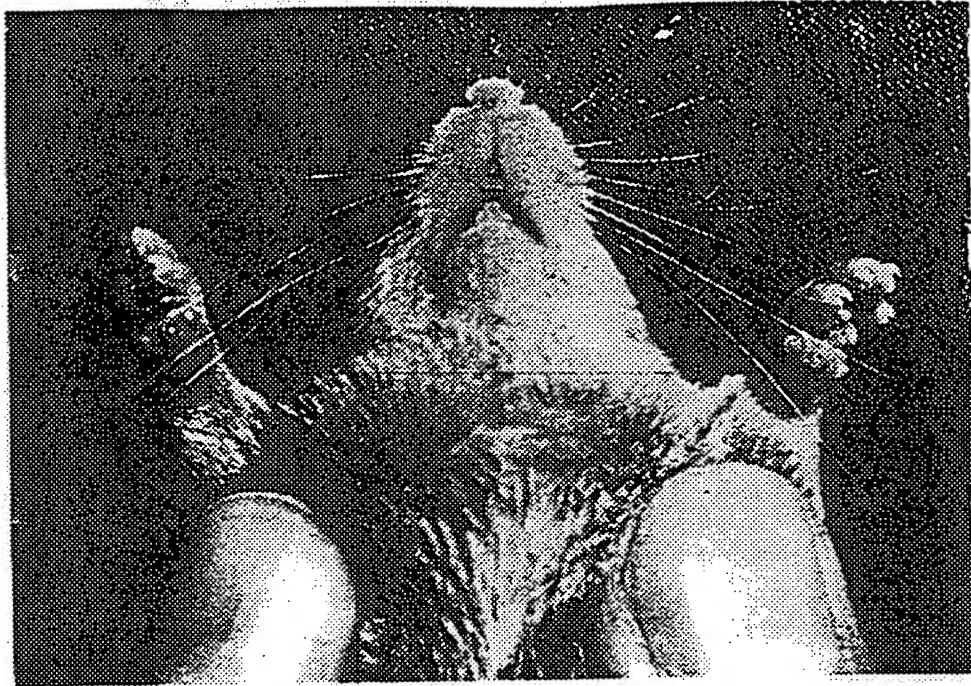


FIG.3B



5/6

FIG. 4A



FIG. 4B

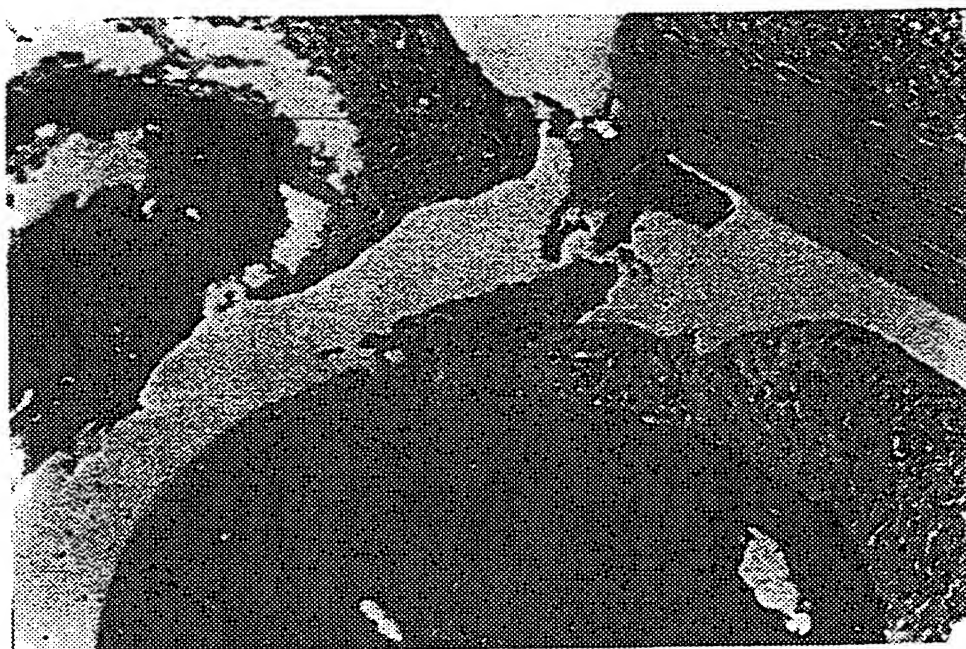
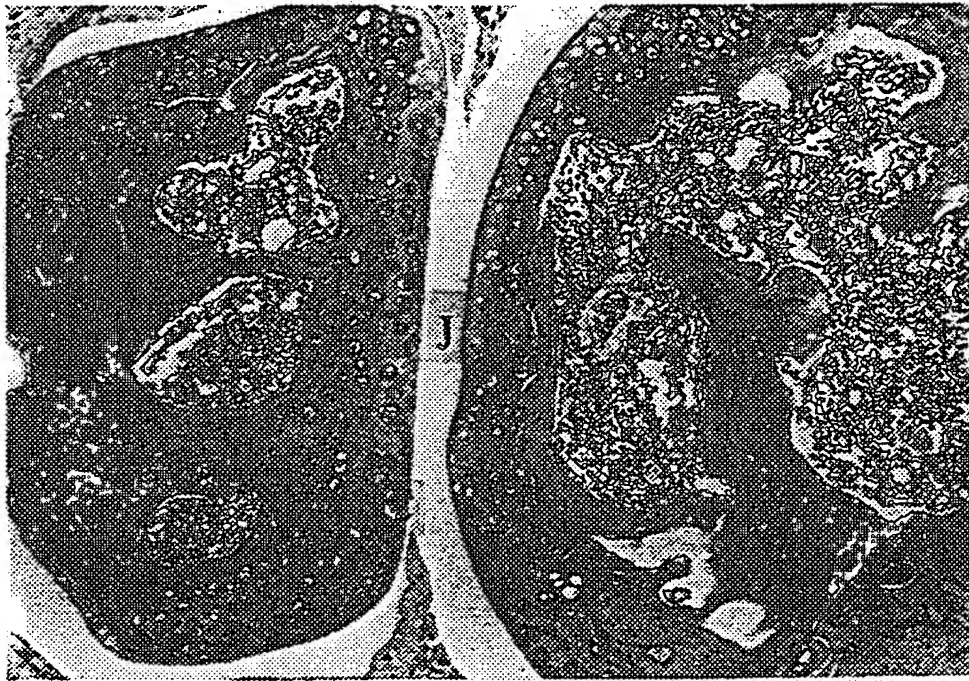


FIG.4C



# INTERNATIONAL SEARCH REPORT

International application No.  
KR 99/00037

## A. CLASSIFICATION OF SUBJECT MATTER

IPC<sup>6</sup>: A 61 K 38/17

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC<sup>6</sup>: A 61 K 38/17

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

WPI, EPODOC, CAS

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5 182 257 A (ZEPPEZAUER et al.) 26 January 1993 (26.01.93), abstract.	1-5
A	Chemical abstracts, Vol.123, No.15, 09 October 1995 (Columbus, OH, USA), page 1027, column 2, abstract No. 196404k, STEMMER, C. et al. "Mapping of B-cell epitopes recognized by antibodies to histones in subsets of juvenile chronic arthritis", Clin Immunol. Immunopathol. 1995, 76(1), 82-9 (Eng.).	1
A	Database WPI on Epoque, week 9533, London:Derwent Publications Ltd., AN 95-248282, PN JP 07-149745 A, 13.06.95), abstract.	1
	----	

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

\* Special categories of cited documents:

„A“ document defining the general state of the art which is not considered to be of particular relevance

„E“ earlier application or patent but published on or after the international filing date

„L“ document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

„O“ document referring to an oral disclosure, use, exhibition or other means

„P“ document published prior to the international filing date but later than the priority date claimed

„T“ later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

„X“ document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

„Y“ document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

„&“ document member of the same patent family

Date of the actual completion of the international search

01 April 1999 (01.04.99)

Date of mailing of the international search report

30 April 1999 (30.04.99)

Name and mailing address of the ISA/AT  
Austrian Patent Office  
Kohlmarkt 8-10; A-1014 Vienna  
Facsimile No. 1/53424/535

Authorized officer

Mosser

Telephone No. 1/53424/435

Form PCT/ISA/210 (second sheet) (July 1998)

# INTERNATIONAL SEARCH REPORT

International application No.

PCT/KR 99/00037

## Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.: 5  
because they relate to subject matter not required to be searched by this Authority, namely:  
  
Remark: Although claim 5 concerns a method for treatment of the human or animal body by therapy (see PCT Rule 39.1 (iv)) the search was carried out and based on the alleged effects.
2. ☐ Claims Nos.:  
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.



INTERNATIONAL SEARCH REPORT  
Information on patent family members

International application No.

KR 99/00037

le Recherchenbericht angeführtes Patentdokument Patent document cited in search report Document de brevet cité dans le rapport de recherche	Datum der Veröffentlichung Publication date Date de publication	Mitglied(er) der Patentfamilie Patent family member(s) Membre(s) de la famille de brevets	Datum der Veröffentlichung Publication date Date de publication
US A	5182257	26-01-1993	
		AT E	15-11-1990
		CA A1	14-03-1999
		DE A1	19-09-1988
		DE CO	06-12-1990
		EP A2	24-07-1998
		EP A3	14-08-1998
		EP B1	31-10-1990
		EP B1	31-09-1994
		JP T2	08-03-1996
		JP B4	25-01-1998
		US A	04-04-1999
		WO A1	18-07-1998
		DE A1	05-09-1998
		AT E	15-10-1994
		DE CO	27-10-1994
		DE T2	24-05-1995
		EP A1	17-10-1990

**THIS PAGE BLANK (USPTO)**